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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,870	08/10/2006	Michal Svoboda	J507-006 US	4078

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NOTARO AND MICHALOS
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SUITE 110
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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	**PAPER NUMBER**
1618	
MAIL DATE	**DELIVERY MODE**
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,870	SVOBODA ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt of Applicant's arguments dated 5/30/2008 is acknowledged.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motola et al. US 5024997 (Motola) in view of EP 0 490 193 (EP), machine translation and further in view of Small et al. Pharmacokinetic and Taste Evaluation of Ibuprofen (Motrin®) 800mg Tablets in Extemporaneous Solution, *Journal of Reumatology* 1988 Feb; 15(2):345-7 (Small).

Motola teaches palatable ibuprofen aqueous base solutions which contain dissolved therein ibuprofen, hydroxypropyl beta cyclodextrin and a sweetening agent; the sweetening agent may include sorbitol and glycerin (see examples). Such solutions have utility in pharmaceutical preparations for oral administration (see abstract and examples). The amount of ibuprofen is 2% w/v (see examples 1-5). The ratio between ibuprofen and cyclodextrin compound is about 1:12 (see examples 1-4). Sorbitol is used in the solution (examples 1-4). Further, Motola teaches that the hydroxypropyl beta cyclodextrin was added and dissolved therein. The solution was heated to 50ºC. while mixing and the ibuprofen was added. Mixing was continued until the solution was clear while maintaining 50º C.

Motola discloses ibuprofen; however, the disclosure is deficient in disclosing the specified enantiomer of ibuprofen.

EP teaches complexes of S(+)-ibuprofen and hydroxypropyl beta-cyclodextrin in a weight ratio of 0,01 - 2,0. Said complexes can be used in syrups (see example 10). The reference teaches the use of lemon flavor in the composition.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the ibuprofen enantiomer because EP teaches that under physiological conditions it was found that the water solubility of S (+), Ibuprofen beta - Cyclodextrin complex has a better solubility than ibuprofen itself and that the unwanted smell, taste and the disturbing effect on the mucous membrane diaphragm of the Ibuprofens are decreased (see page 5 of the machine translation).

EP does not disclose the reason of using the lemon flavor.

Small teaches a study to determine the pharmacokinetic and palatability characteristics of ibuprofen. Changes in T_{max}, peak concentration achieved and area under curve were noted with kinds of flavors such as coca-cola solution. A conclusion was made that cherry syrup solution and orange juice are preferred for palatability and bioavailability of ibuprofen.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a citrus flavor to induce palatability and ensure bioavailability of the drug in the form of syrup. Thus the skilled artisan would have excellent expectation of a preparing a palatable syrup containing S(+)-ibuprofen, hydroxypropyl beta-cyclodextrin which is palatable and have good bioavailability. The expected result would be a palatable syrup containing S(+)-ibuprofen, hydroxypropyl beta-cyclodextrin, water and a sweetener.

Response to Arguments

2. Applicant's arguments filed 5/30/2008 have been fully considered but they are not persuasive. Applicant argues that:

- The subject-matter of Claim 1 of the present application clearly differs from that of EP essentially, in more aspects. EP teaches a solid complex of S(+)-ibuprofen with cyclodextrin, prepared by phase-transformation technique, and its optional use for the preparation of a syrup. During the phase-transformation process in EP, S(+)-ibuprofen is melted in an aqueous suspension of a suitable cyclodextrin as a host molecule and after exceeding its melting point a solid crystalline complex is formed.

To respond: The subject matter of claim 1 is a composition that comprises S(+)-ibuprofen, hydroxypropyl beta-cyclodextrin, a sweetener, water, and optionally essential oils. S(+)-ibuprofen and hydroxypropyl beta-cyclodextrin in a weight ratio of 0,01 - 2,0. Said complexes can be used in syrups. Motola teaches palatable ibuprofen aqueous base solutions which contain ibuprofen dissolved therein, hydroxypropyl beta cyclodextrin and a sweetening agent; the sweetening agent may include sorbitol and glycerin. Thus, the subject matter of instant claim 1 is obvious. Applicant also argues the differences in the method of making, however, since claim 1 subject matter is a composition, the method of its making would not be of patentable weight.

- Hydroxypropyl beta-cyclodextrin, the cyclodextrin derivative used in the present application, is mentioned only in Claims 11 and 18 of EP as one of the cyclodextrin derivatives possibly suitable for the preparation of S(+)-ibuprofen-containing solid crystalline complex. Its use for the preparation of syrup is not disclosed or suggested anywhere in EP.

To respond: suggesting the use of beta-cyclodextrin in the claims is enough motivation for a person having ordinary skill in the art to use this derivative to produce liquid ibuprofen.

- The weight ratio of S(+)-ibuprofen to the cyclodextrin derivative in the syrup of Example 10 of EP is 1:6.47. Long-term stability and masking of the unpleasant taste can be affected if the ratio is not adjusted to 1:10 to 1:18. At lower weight ratios the S(+)-ibuprofen starts to segregate from the solution and the taste-masking is incomplete.

To respond: it is within the skills of a person having ordinary skill in the art to optimize ratios and amounts. Note that taste and stability are regular needs in all liquid preparations, these are not something that may surprise the producer of a product. Therefore, the artisan would be able optimize the amounts disclosed by EP.

- Applicant argues the processing temperature in EP that reaches 60°C while the processing temperature in the instant claims is between 15-50°C.

To respond: instant methods do not exclude a melting step, it is noted that EP teaches that S (+) - ibuprofens is an ideal foreign molecule for these integration procedures, there it a low melting point of 50 DEG - 53 DEG C possesses. For the complexation several kinds at cyclodextrins or Cyclodextrin derivative can become used (see highlighted lines in page 3). This temperature of melting overlaps with the degree recited in instant claims.

- The inventors of the present invention have found that by working-up the mixture at lower temperature such undesirable effects of melting and the sticky layer can be avoided.

To respond: Instant claim recite a temperature of 15-50°C, EP teaches that the melting point of the S(+)ibuprofen is 50°C. Thus the meting temperature overlaps.

- No artificial flavors of essential oils were assessed in Motola; in fact only taste acceptability of known beverages after addition of strong ibuprofen tablets was appreciated. No data was collected following S(+)-ibuprofen administration.

To respond: Motola was relied upon for teaching the enantiomer recited in instant claims. However, the instant claims recite the essential oil as an optional ingredient. Hence the claims are correctly rejected.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618